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**Review Article**

# Early life adversities predispose to adult psychopathology

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**Summary**

*Adverse life events in childhood have been associated with a wide range of mental disorders during adulthood. Literature supports the hypothesis of stress-sensitive periods throughout development. Stressful life events may interact with genetic and other vulnerability factors in their influence on the progress of psychiatric disorders. The nature and duration of the traumatic experiences determine the severity of psychopathology in a dose-dependent manner, with different effects on different psychiatric disorders. Severe and cumulative early abuse affects mental health regardless of diagnosis and is expressed with symptoms of cognitive deficits, difficulties in regulating bodily and emotional reactivity, self harming and aggressive behaviors and physical medical conditions. Recent studies outline the neurobiological consequences of early stressful events leading not only to neuroendocrinological and neurotransmitter dysfunctions, but also to structural brain alterations viewed in neuroimaging studies as relative limbic hyperfunction in conjunction with hypofrontality. The pleiotropic effects of early stressful experiences extend to a variety of physical medical conditions caused by the hypothalamic-pituitary adrenal axis dysregulation. In addition, traumatic consequences through transgenerational transmission induce mental health impacts, by means of epigenetic modifications caused by abusive environmental influences. Even though adverse life events during childhood are quite frequent, they usually remain quiescent and from prime psychosocial conditions they arise, after a long time, as biological issues. Common medical and psychiatric disorders in adulthood emerge from conditions that are not detected in childhood.*

*Stressful life events during early neurodevelopmental periods predispose to adult psychopathology. Coordinated efforts are needed in order to identify children at risk of early maltreatment with emphasis on identification of high-risk populations. The implementation of prevention strategies could act compensatory by eliminating risk factors and ultimately changing the final prognosis.*

**Keywords:** trauma, stress, neurodevelopment, psychopathology

## Introduction

In recent years there has been an increased understanding of the importance of early traumatic experiences and their impact on the emergence of psychiatric disorders in adults. Traumatic events in the early stages of life predispose to a wide range of psychiatric disorders.

In the 1950s-60s, the founder of the concept of prime experiences and their effects on behavioural and physical adaptation, Seymour Levine, pioneered the research in developmental neurobiology and evidenced the long-term effects of early experiences on the functioning of the endocrine, immune and central nervous system and demonstrated that early life experiences shape the behaviour and physiology of stress-related systems.

Mental health professionals initially had difficulty in recognizing the role of early traumatic experiences in psychiatric disorders. The 20th century began with Freud having disavowed his initial discovery that most of his hysterical patients had been sexually abused, convinced that these confessions represented fantasies. By the end of the century, however, epidemiological studies revealed the alarming degree of child abuse-neglect, and the pressure on the scientific community to respond to these findings originated from women's movements. The diagnosis of post-traumatic stress disorder in 1980 referred to Vietnam veterans, not abused children. When reports of abuse were truly documented, their effects were interpreted as symptoms of psychiatric disorders of biological origin, because the scientific community was not receptive to foresee the long-term effects of early trauma, particularly when it affected the developing brain.

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**Forms and interrelationships of early traumatic experiences**

The Adverse Childhood Experiences (ACE) Study was one of the largest studies investigating the relationship between childhood abuse and its ultimate effects on physical and mental health (1). Results emerged from the collaboration between the Centers for Disease Control & Prevention (CDC) and the Department of Preventive Medicine at Kaiser Permanente (KP) in San Diego. More than 17,000 people participated in the study and more than 50 scientific articles and 100 presentations have been made based on the results of the study.

The 10 forms of early traumatic experiences according to the study above were child abuse (emotional, physical, sexual), neglect (emotional, physical), witnessing domestic violence, parental intra-marital conflicts, parental substance abuse, parental psychiatric disorder, offending behaviour by family members, parental deprivation (divorce; death-disappearance), life-threatening physical childhood illness and extreme economic hardship.

Investigating the intercorrelations between early traumatic experiences, a study (2) of 8629 adults in California showed that 2/3 of the subjects reported at least 1 traumatic experience out of 10 included. The observed number of respondents with high scores of traumatic experiences was significantly higher than the expected, assuming that traumatic factors were independent, differently these factors were interrelated and coexisted, which must be taken into account in order to determine their short- and long-term cumulative effects on behavior, emotional and social adjustment, and physical health. Percentages of 81%-98% of individuals with 1 traumatic experience reported 1 additional, and the presence of 1 traumatic experience significantly increased the likelihood of an additional by 2-18 times. Strong graded associations have been reported between many categories of trauma and health problems (smoking, drug and alcohol use, unwanted pregnancy, STDs, self-destructive attempts, etc.). Therefore, adults who reported experience of one traumatic factor were likely to have been exposed to others, which should be taken into account in research studies, prevention programmes and in the documentation of social and legal consequences.

**Epidemiological data: Associations with onset and prognosis of psychiatric disorders**

A retrospective study (3) of 9282 US adults examined the associations between 12 recollected early traumatic experiences that occurred before the age of 18 years old (3 types of parental deprivation: death, divorce, other forms of parental-caregiver separation, 4 types of parental dysfunction: parental psychiatric disorder, substance abuse, violence and delinquency, 3 types of abuse: physical and sexual abuse and neglect, and 2 other types of early traumatic experiences: life-threatening physical illness in childhood and extreme economic hardship), regarding the first emergence of any of the 20 psychiatric disorders per DSM-IV. 53.4% of the sample reported at least 1 traumatic experience. The co-occurrence of multiple traumatic experiences was the commonest of reports at rates ranging from 51.2% in those reporting death of a parent to 95.1% in those reporting neglect. The multivariate predictive model estimating only the number, not the type of traumatic factor, demonstrated an increase in the relative risk of emergence of any mental disorder along with the number of traumatic factors (from 1.3 for 1 traumatic factor compared to none, to 3.4 for 6 and 3.2 for 7 or more factors). The predictive model that included the types and number of traumatic factors better explained the data in relation to the emergence of psychiatric disorders. The 4 types of parental dysfunction and the 3 types of abuse had the largest associations, and multiple traumatic experiences had significant subadditive associations regarding the onset of psychiatric disorders. Traumatic factors collectively explained 32.4% of all psychiatric disorders (41.2% of conduct disorders, 32.4% of anxiety disorders, 26.2% of mood disorders, and 21% of substance use disorders). Also, traumatic factors explained a higher proportion of psychiatric disorders with onset during childhood (44.6%) than during adolescence (32%) and adulthood (28.6%) [aged 20-29] and 25,9% [aged >30]) and this decrease was due to a decrease in the onset rates of induced mood disorders, and less so for anxiety disorders, from childhood to adulthood, while substance use disorders remained stable regarding age of onset.

Another large epidemiological study (4) of 51,945 adults from 21 countries reported similar findings, with high prevalence and interactions between early traumatic experiences. Traumatic experiences stemming from domestic-parental dysfunction were strongly associated with subsequent psychiatric disorders, with co-occurring traumatic experiences having significant subadditive associations and low specificity towards a particular psychiatric disorder. Overall, 29.8% of all psychiatric disorders from all countries were attributed to the presence of early traumatic experiences. Similar rates of early traumatic experiences were reported among high (38.4%), high-middle (38.9%) and low-middle (39.1%) income countries. Death of a parent was the most common traumatic factor (11-14.8%), followed by physical abuse (5.3-10.8%), domestic violence (4.2-7.8%) and parental psychiatric disorder (5.3-6.7%). The coexistence of multiple traumatic factors was common (59.3-66.2%), with an average number for more than 2 factors of 2.5-2.9. Traumatic factors referring to family dysfunction (parental psychiatric disorder, substance abuse, offending behaviour, domestic violence, physical, sexual abuse and neglect) were strongly associated. In conclusion, eliminating early traumatic factors, would result in a 22.9% reduction in mood disorders, 31% in anxiety disorders, 41.6% in conduct disorders, and 27.5% in substance use disorders.

In another epidemiological study (5) of a representative sample of 5,692 US adults, the associations of early traumatic experiences with long-term outcome of psychiatric disorders (episode duration, number of relapses) versus first emergence, reported that 2/3 of early-life traumatic experiences were associated with long-term outcome of psychiatric disorders in the binomial model, but most associations, with the exception of physical and sexual abuse, were non-statistically significant in the multivariate model, with weak ORs

(1.1-1.2). A weak dose-dependent association also emerged between the number of early traumatic experiences and the long-term outcome of psychiatric disorders. The predictive model that best explained the long-term outcome of psychiatric disorders was the type of family-parental dysfunction among the traumatic factors (i.e., parental psychiatric disorder, physical and sexual abuse and neglect) not the number of factors, whereas neither the type of other traumatic factors (other than family-parental dysfunction) nor their number explained the outcome. Allocation according to psychiatric disorder suggested that traumatic factors of the type of parental dysfunction were associated with the outcome of emotional, anxiety and substance use disorders but not with conduct disorders. Specifically, parental substance use disorders were more strongly associated with substance use disorders in participants than with other psychiatric disorders, and physical abuse was more strongly associated with emotional disorders than with other disorders. Other types of traumatic factors besides parental dysfunction were associated with the outcome of conduct disorders, but not with the outcome of emotional, anxiety, and substance use disorders. Significant associations of traumatic factors with the outcome of psychiatric disorders were evidenced throughout the lifespan of the participants, even in the elderly. The effects of traumatic factors on the outcome of psychiatric disorders were stronger for affective and substance use disorders than for anxiety disorders. Overall, the effects of co-occurring traumatic experiences of the parental dysfunction type were subadditive, suggesting that a simple cumulative calculation is deemed insufficient to capture the true effects of multiple traumatic experiences. In a simulation model, removing all traumatic factors produced a 1.6% increase (from 8.3 years on average to 8.4 years) in the mean duration between the most recent episode and the interview, suggesting that while the associations of traumatic factors with psychiatric disorder outcome are statistically significant, their substantive clinical importance is modest. The most significant effects with the removal of all traumatic factors were recorded for affective disorders (5% increase in the time since the most recent episode). In conclusion, because of the stronger associations of early traumatic experiences with the onset of psychiatric disorders than with their outcome, a focus on primary rather than secondary prevention was suggested.

Another epidemiological study (6) on a sample of 6,483 adolescents [13-17 years old] in the USA reported that 58.3% of them had been exposed to at least 1 adverse experience, with 59.7% reporting exposure to multiple adversities. Rates of co-occurrence of multiple traumatic factors ranged from 70.9% in cases of divorce to 97.9% in cases of neglect. Strong associations emerged between early adversities of the type of family dysfunction and the onset of psychiatric disorders. The multivariate model considering the number, not the type of factors, showed an increase in correlations from 1.8 for 1 factor to 4.6 for 6 factors. 8 types of traumatic factors were associated with the onset of conduct and substance use disorders, 6 with mental distress and phobic disorders. The family dysfunction type was associated with the onset of phobic disorders, mental distress and substance use disorders, not with behavioral disorders, and the other types of traumatic factors were associated with the onset of phobic disorders, mental distress and behavioral disorders but not with substance use disorders. Traumatic factors explained 28.2% of all psychiatric disorders, namely 15.7% of phobic disorders, 32.2% of mental distress disorders, 40.7% of conduct disorders and 34.4% of substance use disorders. Traumatic factors of the family dysfunction type were more important than other factors (23.7% versus 6.4%). The most significant factors were parental offending (9.2%) and parental psychiatric illness (6.8%).

## Clinical and psychopathological implications

The consequences of early-life trauma depend on factors such as the age at which the traumatic event occurs, the duration of the traumatic experience, the identity of the perpetrator, the presence of a competent caregiver, the type and severity of trauma, and the provided interventions.

Given the high prevalence of traumatic experiences (up to more than 1/3 of the general population) this can be considered a determinant of public general and mental health. Adults with a history of more than 6 traumatic experiences during childhood had an increased likelihood to die 20 years earlier compared to those without such a history. Childhood abuse and neglect are non-specific risk factors for a wide range of psychiatric disorders. In childhood, conduct disorders, ADHD, oppositional defiant disorder are mentioned. Strong associations have been reported between childhood trauma and mood and anxiety disorders in adulthood, including unipolar depression, bipolar disorder, generalized anxiety and panic disorder, phobias and post-traumatic stress disorder. In addition, early traumatic experiences are associated with increased rates of schizophrenia, social functioning deficits, dissociative and eating disorders, and personality disorders. An association between abuse during childhood and subsequent substance abuse has also been reported, and that traumatic experience during childhood dramatically increases the risk of future self-destructive attempts. Dube et al. (2001) reported a two- to fivefold increased risk for lifetime self-destructive attempts in primary care patients with a history of childhood abuse (7).

Traumatic experiences during childhood also affect the clinical course of psychiatric disorders with failure to recover and progression to chronicity (8). In a 5-year prospective study among patients with major depression, those with a positive history of early-life trauma were less likely to recover than those without a history of trauma. The chronicity of depressive episodes has been linked to childhood trauma, and both domestic violence and sexual abuse were predictors of failure to recover during a 12-month follow-up in patients with a major depressive episode (9,10).

Exposure to multiple traumatic factors during childhood has negative effects on mental health in adulthood. The greater the number of traumatic experiences, the greater the risk of a major depressive episode and increased severity, frequency and duration of abuse increase the likelihood of depression (11,12,13,85).

**T**he association between early-life trauma and psychopathology already exists since childhood and in a pro-

spective study of 676 children with major depression who had suffered severe abuse and/or neglect before the age of 11 years, compared to 520 children without abuse or neglect, traumatic experiences were associated with an increased likelihood of major depression early in adulthood, and children who suffered multiple forms of abuse had an increased risk of chronic depression. Compared to controls, abused children had an early onset of depression and increased comorbidity. Generally, in terms of psychopathological effects, the earlier the trauma, the greater the severity of these effects. Depressive symptoms are of increased severity when the abuse occurs before the age of 12 years of age (14,15).

Early parental deprivation is also a risk factor for depression and other psychiatric disorders (16). A study compared rates of early parental deprivation before the age of 17 years old in patients with major depression, bipolar disorder, and schizophrenia with healthy controls and concluded that parental loss during childhood increased the likelihood of a major depressive episode during adulthood and the effects due to permanent separation were more severe compared with those caused by death, as well as whether the separation occurred before the age of 9 years old (17). Also, early parental deprivation was associated with increased rates of bipolar disorder (18).

Social functioning impairments have been identified as consequences of abuse, such as insecure attachment, avoidance of social relationships and deficits in social-interpersonal functioning, as well as difficulties in emotional and affective self-regulation. Studies report that patients who have been abused during childhood are more likely to be hospitalized in psychiatric hospitals, earlier, for longer periods of time and more frequently, to receive combinations of prescription medications, to exhibit parasuicide activity and suicidality, and to have increased symptom severity (19). Alvarez et al. examined 102 patients with schizophrenia, bipolar and schizoaffective disorder and reported that 47.5% of them had been abused in childhood and were twice as likely to have been hospitalized, and patients with sexual abuse were twice as likely to have attempted suicide (20). At the psychological level, researchers have focused on mechanisms that may mediate between early-life trauma and future psychiatric problems, including attachment procedures, dissociation, psychodynamic defenses and coping mechanisms, as well as social support deficits and re-victimisation (21).

Patients with bipolar disorder are reported to be most vulnerable to the effects of early-life trauma, with 30-50% of them reporting childhood trauma, usually emotional abuse, which usually results in frequent relapses, combined with lower levels of functioning and poor compliance with treatment. Bipolar patients with records of physical or sexual abuse usually have more severe manic episodes, early disease onset, increased comorbidity, and greater likelihood of suicidal behaviour (22). These individuals who experience difficulties in interpersonal relationships tend to be more isolated, more resistant to treatment, and more likely to relapse (23).

Patients with borderline personality disorder also report much higher rates of childhood trauma compared with patients with other psychiatric disorders (24). There is evidence to support that posttraumatic stress disorder in adults intervenes between childhood abuse and the development of a wide range of psychopathological disorders (25,26). 25% of individuals who experience early-life trauma present with PTSD symptoms, and the presence of a psychiatric disorder increases the likelihood of PTSD as well as the likelihood of exposure to early-life trauma (27,28).

A dose-dependent effect on the consequences of early-life trauma has been reported for schizophrenia and post-traumatic stress disorder. Studies comparing the effects of trauma among different psychiatric disorders report specific associations depending on the psychiatric disorder, but also associations between abuse and specific symptoms such as hallucinations across a wide range of diagnostic entities (86). Studies comparing adult psychiatric patients with normal controls suggest that the former are characterized by early stressors during childhood, before the onset of adolescence, but not during adulthood. Although such associations are not causal, the fact that the genetic component in psychiatric disorders is responsible in up to 50% means that other factors are involved, including possibly early stressors, with or without the involvement of other third mediating factors. It is speculated that early stressors interact with psychiatric disorder-specific predisposing factors cumulatively with genetic factors or delimiting potential coping mechanisms (29,30).

Studies report that people who have suffered early-life trauma have multiple psychiatric disorders (comorbidity). The term 'trauma spectrum disorders' is used to describe these conditions (31) that arise from the enduring neurodevelopmental consequences of early traumatic experiences.

Furthermore, a study showed a graded association between the number of traumatic experiences and anxiety and emotional symptoms, as well as the presence of hallucinations and aggressive behaviour. A strong correlation was found between early-life trauma and future use and abuse of drugs and alcohol. Also significant were the effects on physical health (an increased number of traumatic experiences led to increased likelihood of obesity, but also multiple physical health problems - hypertension, hyperlipidemia, metabolic disorders, asthma, infections, etc.). The graded association between the number of stressful experiences and various psychopathological and physical diseases, as well as the number of comorbid conditions, parallels the cumulative effects of stress exposure inflicting structural and functional changes in the developing brain (32).

## Early-life trauma and psychosis

### I. Epidemiological studies

Recent research data support the existence of a correlation between early traumatic experiences and psychosis. A 2009 review (33) highlighted 11 studies reporting a significant association between childhood abuse and the development of psychosis. A dose-dependent association was reported in 9 out of 11 studies. A prospective study in the Netherlands (34) reported that individuals who had been

abused in childhood were 9 times more likely to develop psychosis compared to non-abused individuals (with OR=2 for mild abuse and OR=48.4 for severe abuse). There was also reference on the relationship between childhood abuse and the content of delusions and hallucinations, and research validated the reliability of schizophrenic patients' recollections about the abuse they had suffered. Another review concluded about the evidence of an association between childhood sexual abuse and psychosis, and this association is as strong, perhaps even stronger, than the association for other psychiatric disorders. It is suggested that childhood sexual abuse appears to have a specific effect on the likelihood of hallucinations, while difficulties in social relationships and chronic victimization (bullying) increase the likelihood of paranoid delusions.

Approaching the biopsychosocial model by means of etiopathogenesis, the traumatogenic neurodevelopmental model has been proposed (35), according to which the structural and biochemical alterations found in the brains of schizophrenic patients have also been demonstrated in the brains of abused children. Patients with psychotic disorders and a history of early-life trauma presented with more dissociative symptoms compared to psychotic patients without a history of trauma, and exposure to multiple traumatic stimuli rather than single, also increased the likelihood of psychotic disorder.

A prospective study investigating the existence of a causal association between early-life trauma and psychosis in 1,112 adolescents aged 13-16 reported a bidirectional association with early trauma predicting psychotic experiences and vice versa. However, when the study was strictly limited to psychotic symptoms that occurred after exposure to traumatic experiences, they were found to be a strong predictor of new psychotic symptoms. A dose-dependent relationship was also detected between severity of traumatic experiences and risk of psychotic symptoms and also cessation of traumatic experiences predicted remission of psychotic symptoms (36).

A recent meta-analysis of 41 studies including patient-control, prospective- and cross-sectional cohort studies demonstrated significant associations between early-life trauma and psychosis, with an overall OR = 2.78. In the patient-control studies it was argued that psychotic patients were 2.72 times more likely to have been exposed to traumatic experiences than controls. Cross-sectional cohort studies demonstrated OR = 2.99 and prospective studies OR = 2.75. In summary, the estimated population attributable risk was 33% (16%-47%). This means that traumatic experiences increased the risk of psychosis, and if these factors were to be eliminated, under the condition of causality, the number of psychotic patients would decrease by 33% (33). Still according to the meta-analysis all types of traumatic experiences were associated with an increased risk of psychosis, with no one type being more predisposing. It is suggested that other variables may be more strongly associated such as age of exposure to trauma and exposure to multiple traumatic events. However, the type of traumatic experiences modifies the emergence of specific psychotic symptoms. The studies included in the meta-analysis estimated confounding factors (psychiatric comorbidity, ethnicity, education, IQ, cannabis and other drug use, genetic predisposition, urbanization).

## II. Etiopathogenesis of psychosis in relation to trauma

A recent genome-wide study (37) examining genome DNA methylation alterations as a result of early-life trauma demonstrated differentially methylated promoters in individuals with a history of abuse compared with controls. The effects were more pronounced with genes involved in cellular / neuronal plasticity and were consequently implicated in increased risk for psychiatric disorders.

Another study has highlighted mediating biological factors in the relationship between early-life adversities and psychotic symptoms (38) reporting that psychotic symptoms were associated with the interaction of traumatic experiences and the Val66Met polymorphism of BDNF. Carriers of the Met polymorphism presented with more positive psychotic symptoms when exposed to childhood abuse than Val/Val carriers, suggesting a gene-environment interaction as partially responsible for modulating the response to early-life trauma.

Psychological theories argue that childhood exposure to abuse engenders negative cognitive schemas of self and world that result in a sense of weakness and vulnerability about the self and the evaluation of neutral stimuli as negative and the world as dangerous, which favours exogenous causal attributions that can eventually lead to misinterpretations and paranoid delusions. In this sense, contemporary theories of the biological consequences of early-life trauma lend further credence to the existence of an enduring psychological vulnerability (39-41). When exposure to stressors persists, the stressor-induced glucocorticoid release becomes chronic and leads to permanent alterations in the function of the HPA axis (42), which in turn may lead to dysfunction of the dopaminergic system (increased dopamine release and increased dopaminergic receptor concentrations), which is thought to be important for the attribution of salience to stressful stimuli and thus facilitates positive psychotic symptoms

### Neurobiological effects of early stressors

Early-life trauma programs the stress system to have an exaggerated and prolonged response to future stressful stimuli. Exposure of the developing brain to the neuroendocrine products of stress brings about consequences by altering gene expression, neurotrophic factors, myelination, and processes of neurogenesis and synaptogenesis. The effects of early trauma on the developing brain depend on the timing of the traumatic event, the vulnerability of brain regions and genetic factors.

Since 1990, neurobiological and neuroendocrinological studies have highlighted the effects of chronic stress on brain development. The most accepted theory of changes in brain structures suggests that early stressors interfere with mechanisms of neurogenesis, synapse overproduction, syn-

apse and receptor pruning. Glucocorticoids released during stress may compromise neuronal plasticity. Brain regions with elevated concentrations of glucocorticoid receptors characterized by prolonged developmental phases after birth have greater vulnerability to stress. Common features of brain areas of increased vulnerability to stress are characterized by prolonged postnatal neurodevelopmental period, increased glucocorticoid receptor density and some degree of neurogenesis after birth.

From a neurobiological point of view, exposure to early stressors programs the body to exhibit increased stress responsiveness that is detrimental to important neurodevelopmental processes during specific developmentally sensitive periods (43). Structural and functional effects of early stressors have been identified such as reduced corpus callosum size, left neocortex underdevelopment, differentiation in the hippocampus and amygdala, increased electrophysiological activity in limbic structures, and reduced functional activity of the cerebellar vermis. This alternative neurobiological development may induce psychiatric and behavioral disorders.

In the hippocampus early stress inhibits synaptogenesis but not synapse pruning so the final result is a synapse deficit. There are conflicting findings in studies as to the effects of early abuse on the hippocampus with some studies reporting reduced hippocampal size in adults who were traumatized during childhood, but other studies failing to show significant differences in hippocampal size between abused children and healthy controls. Alterations in hippocampal neurodevelopment may lead to the emergence of symptoms of post-traumatic stress disorder, with predominantly dissociative symptomatology rather than symptoms of impaired memory function.

Studies have associated changes in electrophysiological activity in temporolimbic structures (with EEG findings) with increased suicidal and aggressive behaviour. It is suggested that early stress induces permanent alterations in the structure of GABA-A receptor complexes in the amygdala, reducing both the density of central benzodiazepine receptors and affinity, which may lead to epileptiform activity in limbic structures termed 'limbic irritability' (illusions, transient hallucinations, automatisms, dissociative phenomena) (44). It also induces increased dopamine levels and decreased serotonin levels in the amygdala and the caudate.

Studies also report that early stress causes gender-dependent changes in the size of the corpus callosum, in particular a reduction in the size of the middle regions of the corpus callosum, especially in boys who have been severely abused and neglected. It appeared that the effect of neglect was detrimental in the development of corpus callosum in boys, same as the effect of sexual abuse in girls (45).

In addition, early stress brings about alterations in prefrontal development resulting in early maturation but reduced final performance. Comparatively, a study between right-handed children who had been abused and normal controls demonstrated significant underdevelopment of the left hemisphere, whereas the right hemisphere had a similar degree of development (46). Early stress also affects monoaminergic neurotransmitter pathways by modulating their development differently between right and left hemisphere and lead to a decrease in the expression of a2 noradrenergic receptors in the locus coeruleus, resulting in a loss of backward inhibition of stress-induced noradrenergic activity, as well as alterations in serotonergic and GABAergic neurotransmitter pathways. In combination with various hormonal effects as to gender (47) during neurodevelopment, the consequences of childhood trauma are also differentiated (estrogens in women have an epileptogenic effect on limbic structures, particularly if they are already sensitized, progesterone reduces epileptogenic activity but may induce depression, and testosterone in men has an antiepileptic effect through NMDA receptor antagonism). Researchers have argued that exposure to elevated glucocorticoid levels prenatally is associated with low birth weight of newborns and induces a permanent increase in corticosteroid levels, which is associated with an increased risk of cardiovascular disease and type II diabetes mellitus. After birth, abuse-neglect triggers a sequence of stress responses that organizes the brain to develop towards an alternative survival pathway, but which is associated with increased risk of developing major medical and psychiatric disorders (48).

The combination of genetic influences, early trauma and ongoing stress ultimately determines the responsiveness of the neural stress pathways and the vulnerability to psychiatric disorders. Early stressors cause long-term effects with permanent sensitization of the neuronal stress pathways with increased responsiveness, decreased expression of cortisol receptors in the hippocampus and increased expression of corticotropin releasing hormone in the hypothalamus, thereby causing long-term dysfunction of the HPA axis. Women who had suffered early abuse, with and without depression, had a significantly higher ACTH response to stressful stimuli, compared with depressed women without early abuse and with healthy controls (42). Depression with a history of early-life trauma represents a distinct endophenotype (49). Also in the dexamethasone- CRH test in individuals with early-life trauma, glucocorticoid resistance is demonstrated. Carpenter et al. (50) argued that a history of early-life trauma, particularly physical abuse before the age of 6 years, is predictive of increased corticotropin-CRH releasing hormone concentrations in CSF, more so than in depression, and recently Heim,Young, et al. (2009) reported decreased CSF oxytocin concentrations in individuals with exposure to multiple abuse, leading to an increased likelihood of anxiety symptomatology, but also decreased capacity for close interpersonal relationships (51). Dysfunction in limbic, hippocampal, amygdala and medial prefrontal cortex structures induces anxiety symptomatology and disturbances in emotion regulation.

**Sensitive neurodevelopmental periods**

Early adversities refer to exposure to one or multiple events during childhood that exceed the ability to manage difficulties and lead to prolonged stressful situations. High or persistently elevated levels of stress can impair brain development and affect mental and physical health. Epidemiological studies report that childhood trauma explains about 32% of adult psychiatric disorders and 44% of childhood-onset

psychiatric disorders.

The sequence of early stressors depends on the type of early-life trauma, the number of traumatic agents and especially the age at which trauma occurred. For example, adults who were sexually abused in childhood after the age of 12 years old were 10 times more likely to experience severe symptoms of posttraumatic stress disorder than individuals who were abused before the age of 12 years (14). Studies regarding sensitive neurodevelopmental periods (44) emphasize on timing when traumatic stress occurs and concurrently affects rapidly developing brain regions. Thus, sexual abuse at ages 3-5 years old and 11-13 years old was associated with smaller hippocampal size. When the abuse occurred at ages 9-10 and 14-16 the dysfunction involved the corpus callosum and prefrontal cortex respectively (52). In conclusion, it was argued that brain areas that underwent extensive neurodevelopment after birth were particularly sensitive to the long-term effects of stress.

**Effects of early stressors on cognitive and emotional functioning**

Lower general intelligence, lower academic performance and increased need for individualized educational programs have been recorded for children who have experienced early stressors (early institutionalization, neglect or abuse). Smaller brain size, reduced hemispheric integration, and smaller corpus callosum size are some neural structural correlates of the generalized deficit in cognitive functions induced by early stressors.

Studies have shown that children who had been neglected had a lower IQ score than children who had not. Significant differences were also found across a range of cognitive functions including vocabulary, memory, learning, attention and executive functions (53). Increased severity of abuse was associated with lower IQ score. Early onset and longer duration of abuse was associated with reduced brain size, where there was a correlation between gray matter volume and IQ score. In cases of early institutionalization, impaired psychomotor development along with cognitive deficits was recorded and the total duration of institutionalization was associated with the degree of cognitive deficit. Prolonged temporal gray matter development in the associative regions (posterior prefrontal and superior temporal gyrus) carries an increased risk for potential impairments contributing to cognitive deficits.

Cognitive deficits in executive functions have often been found in individuals exposed to early stressors (54,55). Studies report impaired ability to inhibit spontaneous response in individuals with a history of exposure to early stressors, as well as in female students with a history of sexual abuse. It has been reported that even in individuals with a high level of functioning, the responsible frontal neurocircuits may be affected by exposure to early stressors. Planning deficits in children who have been subjected to early institutionalization have been associated with smaller cerebellar size due to prolonged neurodevelopmental time, also considered more vulnerable to the effects of exposure to early stressors.

Recent studies have revealed dysfunction in reward neuronal circuits in adults with a history of exposure to early stressors. Patients with a history of abuse, compared to normal controls, were characterized by reduced activation of left basal ganglia structures associated with reward expectancy. This reduced activation was related to the reward expectancy component. In conclusion, long-term and unpredictable stressors lead to desensitization of the mesolimbic dopaminergic pathways (reduced phasic dopaminergic neurotransmission) involved in desire-motivation. This can lead to both anhedonia increasing the likelihood of mood disorders, and novelty seeking that can lead to maladaptive behaviors (substance abuse, suicidality, etc.). Researchers argue that these behaviours are attempts to alleviate dysphoric emotions despite negative reinforcement, i.e. a vicious cycle that characterizes lives of abused individuals and, through the maladaptive management strategies they adopt, due to their cognitive and emotional deficits, increase the risk of re-victimisation.

Children who have been abused and neglected have impaired recognition and response to facial expressions of negative emotion (anger). Recognition and understanding of emotion depends on the amygdala and its projections to temporal structures. Increased amygdala size and hyperresponsiveness to negative stimuli observed in individuals exposed to early stressors pose a risk for later psychopathology. Children who have been abused and suffered from PTSD had reduced gray matter volume in the left superior temporal gyrus (area responsible for speech and communication) and a study reported a 14% reduction in gray matter in the left superior temporal gyrus in adults with a history of parental verbal abuse. Children who have been abused display selective attention and have difficulty disengaging from threatening stimuli that include facial and vocal expressions that suggest anger or fear. No similar difficulty is found with positive emotions. Even if children exposed to early stressors are removed from the harmful environment, emotional deficits usually do not improve and are certainly considered more resilient than cognitive deficits. Significant difficulties in emotional self-regulation are also found to be a risk for long-term psychopathology in individuals exposed to early stressors associated with dysfunction of brain structures such as the lateral posterior prefrontal cortex and anterior part of cingulate gyrus, as well as connections with limbic structures.

Furthermore, a study indicated a decrease in grey matter volume in the visual cortex in individuals who had been sexually abused before the age of 12. When the abuse was at an age older than 12 years old, the decrease in gray matter volume was in the cerebellum. Physical abuse reduces grey matter volume in the visual cortex and in the fusiform gyrus responsible for facial recognition. Finally, diffusion tensor imaging studies also reported a decrease in white matter, specifically in the inferior longitudinal fasciculus/arcuate fasciculus in the left superior temporal gyrus, and in the left formix, in subjects who had suffered verbal abuse (56).

**The role of genetic predisposition**

Children with a pre-existing psychiatric disorder are at increased risk of being abused and in addition, individuals with genetic vulnerability and a history of early-life trauma tend to develop psychiatric disorders earlier than individuals without a genetic predisposition. The likelihood of a major depressive episode depending on the number of traumatic events is modulated by serotonin transporter polymorphism (57). An epidemiological study of 1,404 twin women evidenced that adult depression depends on genetic predisposition, early-life trauma and recent stressful life events. Genetic and environmental influences during childhood predispose to adult female depression. The more severe the early-life trauma, the more vulnerable the woman appears to the effects of recent life stressors (58).

A study highlighted the protective effects of specific polymorphisms of CRHR1 (corticotropin-releasing hormone receptor) defining the effects of early-life trauma on the risk of depression (59). Heim, Bradley, et al. (2009) reported that the CRH-R1 polymorphism protects males with a history of early-life trauma from depression. Also polymorphism of the glucocorticoid receptor FKBP5 protects against the onset of PTSD symptoms as a consequence of early-life trauma (60). In contrast, allele of the MAOA enzyme gene increases vulnerability to childhood abuse, but also increases the likelihood of future antisocial behavior (61). Recent studies have focused on gene--gene effects to determine the risk of depression after early-life trauma (62). Children with the met allele of the BDNF neurotrophic factor genotype and two short alleles of the serotonin transporter 5-HTTLPR genotype had the highest likelihood of depression, but the vulnerability associated with these two genotypes only applied to maltreated children. Providing social support on time further reduced the risk of depression (63). Similarly, in another study the two short alleles of the serotonin transporter 5-HTTLPR genotype interacted with haplotypes of the CRHR1 genotype in modulating depressive symptoms in maltreated children (64).

**Epigenetic modifications as consequences of early-life trauma**

The environment interacts with the genome and modifies its transcription. These processes during neurodevelopment alter the structure and function of brain regions and predispose to psychopathology. Research reports that early-life trauma induces changes in gene expression through epigenetic modifications that modulate adaptation to stress, brain function, and behavior (65).

In autopsy studies of suicide victims with a history of childhood abuse, researchers have demonstrated the presence of epigenetic modifications – DNA hypermethylation in specific promoter regions in glucocorticoid receptors -NR3C1- in the hippocampus, compared to suicides or normal controls without a history of abuse. They revealed a decrease in transcription capacity and binding to neurotrophic transcription factors (NGFI-A) due to hypermethylation in their promoter regions, resulting in silencing of the genetic locus and increased response to stress. In conclusion, the quality of parental care effectuates epigenetic regulation of glucocorticoid receptor expression in the hippocampus and essentially epigenetically modifies genomic regions involved in the regulation of stress response, increasing vulnerability to the onset of psychopathology (66).

It is suggested that childhood abuse induces a cascade of DNA methylation modifications at multiple regulatory transcription promoter regions across the genome. A recent genomic study identified 362 transcription regulatory sites with alterations in DNA methylation in individuals with a history of abuse compared with healthy controls, mostly involving gene regions implicated in neuronal plasticity, particularly in hippocampal regions (37).

**Therapeutic approaches**

**I**t is estimated that about one-third of maltreated individuals do not develop psychiatric disorders in adulthood and a study by McGloin and Widom claimed that 48% of individuals with a history of childhood abuse and neglect did not develop a psychiatric disorder as adults, but only 22% met the criteria for resilience (67). Another study (68) suggested that resilience in these individuals was related to perceived parental care, social relationships with peers, quality of relationships with adult caregivers, and personality.

The presence of a competent and reliable caregiver is one of the most important factors that separate abused children without long-term developmental complications from those with complications. Better knowledge around issues of 'resilience', including genetic factors and 'vulnerable periods' can guide prevention as well as treatment. Emphasis is placed on primary prevention. Early interventions that foster healthy mental and physical development reduce future problems, while treating problems emerging from early traumatic experiences is much more burdensome and costly with uncertain outcomes. The example of social support for children with early-life trauma suggests that situations of psychological distress can be relieved without pharmaceutical interventions, but with emotional support and psychoeducation (63).

However, when serious complications (psychiatric disorder) occur, more specialized pharmacotherapeutic and psychotherapeutic interventions are necessary. It is suggested that patients presenting with symptoms of major depression in primary care should be screened for the possibility of a history of early-life trauma requiring more specialized treatment to achieve symptoms remission.

It is argued by researchers and clinicians that people who have suffered early trauma have maladaptive cognitive schemas involving trust and safety. The proposed schema therapy (69) attempts to modify existing maladaptive schemas (trust, safety, control, dependence, abandonment, autonomy, avoidance).

Important to the proposed treatments is the recognition that relapse can very easily recur in terms of early-life trauma and therefore the timing of some form of exposure to psychotherapy must be based on scientific evidence,

sound clinical judgment and sensitivity from the therapist. In cases of high severity of early-life trauma, a long-term therapeutic process is usually required and it is very important that the person being treated develops strategies for better emotional management.

Studies report that many forms of psychotherapy are effective in treating adults with a history of early-life trauma. Group psychotherapy has been suggested as effective in reducing symptoms and improving functioning for patients who have experienced childhood sexual abuse (70). However, individuals with more severe psychiatric disorder and more severe trauma usually require more intensive individualized and disorder-specific treatment (71).

Cognitive-behavioural oriented psychotherapies are proposed and Briere (72) has developed a therapeutic model that places greater emphasis on maladaptive cognitive processes and learning emotional self-regulation and suggests the necessity of individualized interventions targeted at the specific problems and life experiences of the individual.

Emotion Focused Therapy (EFT) is also recommended for adults with a history of abuse, which during 20 weeks of individualized psychotherapy handles emotions and the resolution of past and present interpersonal difficulties (73).

For people who have suffered parental deprivation, especially of the mother (due to prolonged absence or death), the Family Bereavement Program (FBP) is recommended, which has better results for older children or adolescents (8-16 years old), focusing on managing emotions and difficulties (74). The program includes a separate group for caregivers and children with the goals of improving the quality of the child-caregiver relationship, reducing caregiver mental health problems, and reducing the likelihood of exposing children to additional negative stimuli. The programme focuses on increasing children's confidence that their carers understand their feelings and reducing the need for children to inhibit the negative expression of emotions associated with bereavement. Craighead and Nemeroff (2005) argue that psychotherapeutic interventions are most effective when they are individualized and specifically targeted to the disorder that is emerging, and also when the individual seeks treatment for the psychological distress caused by the trauma (75). Treatment interventions that simultaneously address the behavioural, emotional, cognitive and neurobiological components of emerging disorders have better outcomes (76).

In terms of biological interventions, CRH receptor antagonists have been proposed to reduce the stress response and improve emotional and anxiety disorders (77), with conflicting results. Interventions in the genome to prevent or reverse epigenetic modifications resulting from early-life trauma remain experimental.

Therapeutic response in patients with major depression treated with CBT was associated with metabolic changes (increased metabolism in the hippocampus and dorsal region of cingulum gyrus and decreased metabolism in the dorsal, ventral and medial prefrontal cortex), whereas treatment and response to SSRIs produced different effects in terms of metabolism in brain regions (78).

As for the choice of the treatment strategy to be followed for each patient, the literature is limited. In depression, the presence or absence of a history of early-life trauma is a prognostic indicator that should guide treatment choices (49, 79) towards a combination of pharmacotherapy and psychotherapy (80). When patients suffer from chronic depression and have a history of early-life trauma, psychotherapy effectuates significant improvement with or without pharmacotherapy, whereas depressed patients without a history of early-life trauma benefit more from pharmacotherapy (81).

## Conclusions

Early traumatic experiences over decades converse from psychosocial conditions into biological diseases and determine the health and quality of life of individuals. According to research and clinical studies, early-life trauma leads to neurobiological stress sensitization in adulthood. These neurobiological consequences contribute to the emergence of psychiatric and general medical morbidity (82).

Areas of research include the gene-environment interactions that mitigate the effects of early-life trauma, as well as the identification of sensitive periods for these effects, epigenetic processes, and the prevention or reversal of the pathological effects of early-life trauma. It remains to be shown whether early traumatic experiences determine the degree and quality of the brain's response to stressors later in life and the course and qualitative nature of these changes in the aging process. Medical diseases commonly recognized in adults are the results of conditions not timely identified in childhood (83). Preventive psychiatry acts in this direction by attempting to identify children at risk for early-life trauma and implement prevention strategies.

Despite the fact that several therapeutic approaches exist for individuals who have suffered early-life trauma, research is needed to identify specific neurobiological treatment targets as well as specific prognostic factors that can determine the choice of treatment strategy based on early developmental, genetic and clinical characteristics. Therapeutic outcomes are expected to be better when treatment is individualized according to the specific psychiatric disorder, the nature of the trauma and the existing genetic and environmental interactions.

## References


1. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998 May;14(4):245-58
2. Dong M, Anda RF, Felitti VJ, Dube SR, Williamson DF, Thompson TJ, Loo CM, Giles WH. The interrelatedness of multiple forms of childhood abuse, neglect, and household dysfunction. Child Abuse Negl. 2004 Jul;28(7):771-84.
3. Green JG, McLaughlin KA, Berglund PA, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. Arch Gen Psychiatry. 2010 Feb;67(2):113-23.
4. Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Aguilar-Gaxiola S, Alhamzawi AO, Alonso J, Angermeyer M, Benjet C, Bromet E, Chatterji S, de Girolamo G, Demyttenaere K, Fayyad J, Florescu S, Gal G, Gureje O, Haro JM, Hu CY, Karam EG, Kawakami N, Lee S, Lépine JP, Ormel J, Posada-Villa J, Sagar R, Tsang A, Ustün TB, Vassilev S, Viana MC, Williams DR. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. Br J Psychiatry. 2010 Nov;197(5):378-85.
5. McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC. Childhood adversities and adult psychopathology in the National Comorbidity Survey Replication (NCS-R) II: Associations with persistence of DSM-IV disorders. Arch Gen Psychiatry 2010 Feb; 67(2): 124–132.
6. McLaughlin KA, Greif Green J, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC. Childhood Adversities and First Onset of Psychiatric Disorders in a National Sample of US Adolescents. Arch Gen Psychiatry. 2012;69(11):1151–1160.
7. Dube SR, Anda RF, Felitti VJ, Chapman DP, Williamson DF, Giles WH. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. JAMA. 2001 Dec 26;286(24):3089-96.
8. Norman RE, Byambaa M, De R, et al. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLoS Med. 2012;9(11):e1001349.
9. Wiersma JE. Childhood adversity and depression. J Clin Psychiatry. 2015 Jul;76(7):e906-7.
10. Klein D. N., Arnow B. A., Barkin J. L., et al. Early adversity in chronic depression: clinical correlates and response to pharmacotherapy. Depression and Anxiety. 2009;26(8):701–710.
11. Wiersma JE, Hovens JG, van Oppen P, Giltay EJ, van Schaik DJ, Beekman AT, Penninx BW. The importance of childhood trauma and childhood life events for chronicity of depression in adults. J Clin Psychiatry. 2009 Jul;70(7):983-9.
12. Liu RT. Childhood Adversities and Depression in Adulthood: Current Findings and Future Directions. Clin Psychol (New York). 2017 Jun;24(2):140-153. doi: 10.1111/cpsp.12190. Epub 2017 Mar 23.
13. Negele A, Kaufhold J, Kallenbach L, et al. Childhood trauma and its relation to chronic depression in adulthood. Depress Res Treat. 2015;2015:1–11.
14. Schoedl AF, Costa MC, Mari JJ, Mello MF, Tyrka AR, Carpenter LL et al. The clinical correlates of reported childhood sexual abuse: an association between age at trauma onset and severity of depression and PTSD in adults. J Child Sex Abus. 2010;19(2):156-70.
15. Widom CS, DuMont K, Czaja SJ. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. Arch Gen Psychiatry. 2007 Jan;64(1):49-56.
16. Tennant C. Parental loss in childhood: its effect in adult life. Arch Gen Psychiatry. 1988;45(11):1045-1050.
17. Agid O, Shapira B, Zislin J, Ritsner M, Hanin B, Murad H, Troudart T, Bloch M, Heresco-Levy U, Lerer B. Environment and vulnerability to major psychiatric illness: a case control study of early parental loss in major depression, bipolar disorder and schizophrenia. Mol Psychiatry. 1999 Mar;4(2):163-72.
18. Mortensen PB, Pedersen CB, Melbye M, Mors O, Ewald H. Individual and familial risk factors for bipolar affective disorders in Denmark. Arch Gen Psychiatry. 2003;60(12):1209–1215.
19. Alameda L, Ferrari C, Baumann PS, et al. Childhood sexual and physical abuse: age at exposure modulates impact on functional outcome in early psychosis patients. Psychol Med. 2015;45(13):2727–2736.
20. Alvarez MJ, Roura P, Osés A, Foguet Q, Solà J, Arrufat FX. Prevalence and clinical impact of childhood trauma in patients with severe mental disorders. J Nerv Ment Dis. 2011 Mar;199(3):156-61.
21. Dillon J., Johnstone L., Longden E. (2014) Trauma, Dissociation, Attachment and Neuroscience: A New Paradigm for Understanding Severe Mental Distress. In: Speed E., Moncrieff J., Rapley M. (eds) De-Medicalizing Misery II. Palgrave Macmillan, London.
22. Etain B, Aas M, Andreassen OA, Lorentzen S, Dieset I, Gard S, Kahn JP, Bellivier F, Leboyer M, Melle I, Henry C. Childhood trauma is associated with severe clinical characteristics of bipolar disorders. J Clin Psychiatry. 2013 Oct;74(10):991-8.
23. Agnew-Blais J, Danese A. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry. 2016 Apr;3(4):342-9.
24. Cattane, N., Rossi, R., Lanfredi, M., & Cattaneo, A. (2017). Borderline personality disorder and childhood trauma: Exploring the affected biological systems and mechanisms. BMC Psychiatry, 17, Article 221.
25. Brietzke E, Kauer Sant'anna M, Jackowski A, Grassi-Oliveira R, Bucker J, Zugman A, Mansur RB, Bressan RA. Impact of childhood stress on psychopathology. Braz J Psychiatry. 2012 Dec;34(4):480-8.
26. Auxéméry Y. L'état de stress post-traumatique comme conséquence de l'interaction entre une susceptibilité génétique individuelle, un évènement traumatogène et un contexte social [Posttraumatic stress disorder (PTSD) as a consequence of the interaction between an individual genetic susceptibility, a traumatogenic event and a social context]. Encephale. 2012 Oct;38(5):373-80. French.
27. Bouras G, Lazaratou E. [Emergence of early childhood trauma in adult psychiatric symptomatology]. Psychiatriki. 2012 Jun;23 Suppl 1:39-48. Greek, Modern. PMID: 22796972.
28. Yehuda R, Davidson J. Post-traumatic Stress Disorder: Ed. Science Press Ltd.; 2000.
29. Pietrek C, Elbert T, Weierstall R, Müller O, Rockstroh B. Childhood adversities in relation to psychiatric disorders. Psychiatry Res. 2013 Mar 30;206(1):103-10.
30. Weber K, Rockstroh B, Borgelt J, Awiszus B, Popov T, Hoffmann K, Schonauer K, Watzl H, Pröpster K. Stress load during childhood affects psychopathology in psychiatric patients. BMC Psychiatry. 2008 Jul 23;8:63.
31. Bremner JD, Wittbrodt MT. Stress, the brain, and trauma spectrum disorders. Int Rev Neurobiol. 2020;152:1-22.
32. Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, Dube SR, Giles WH. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci. 2006 Apr;256(3):174-86.
33. Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, Read J, van Os J, Bentall RP. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr Bull. 2012 Jun;38(4):661-71.
34. Janssen I, Krabbendam L, Bak M et al. Childhood abuse as a risk factor for psychotic experiences. Acta Psychiatr. Scand. 109, 38–45 (2004).
35. Read J, Perry BD, Moskowitz A, Connolly J. The contribution of early traumatic events to schizophrenia in some patients: a traumagenic neurodevelopmental model. Psychiatry. 2001 Winter;64(4):319-45.
36. Kelleher I, Keeley H, Corcoran P, Ramsay H, Wasserman C, Carli V, Sarchiapone M, Hoven C, Wasserman D, Cannon M. Childhood trauma and psychosis in a prospective cohort study: cause, effect, and directionality. Am J Psychiatry. 2013 Jul;170(7):734-41.
37. Labonté B, Suderman M, Maussion G, Navaro L, Yerko V, Mahar I, Bureau A, Mechawar N, Szyf M, Meaney MJ, Turecki G. Genome-wide epigenetic regulation by early-life trauma. Arch Gen Psychiatry. 2012 Jul;69(7):722-31.
38. Alemany S, Arias B, Aguilera M, Villa H, Moya J, Ibáñez MI, Vossen H, Gastó C, Ortet G, Fañanás L: Childhood abuse, the BDNF-Val66Met polymorphism and adult psychotic-like experiences. Br J Psychiatry 2011; 199:38–42.
39. Garety PA, Bebbington P, Fowler D, Freeman D, Kuipers E: Implications for neurobiological research of cognitive models of psychosis: a theoretical paper. Psychol Med 2007; 37: 1377–1391 36.
40. Kuipers E, Garety P, Fowler D, Freeman D, Dunn G, Bebbington P: Cognitive, emotional, and social processes in psychosis: refining cognitive behavioral therapy for persistent positive symptoms. Schizophr Bull 2006; 32(suppl 1):S24–S31 37.
41. Blackwood NJ, Howard RJ, Bentall RP, Murray RM: Cognitive neuropsychiatric models of persecutory delusions. Am J Psychiatry 2001; 158:527–539.

42. Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, Miller AH, Nemeroff CB: Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA 2000; 284:592–597.
43. De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, Frustaci K, Ryan ND, A E. Bennett research award. Developmental traumatology. Part II: brain development. Biol Psychiatry 1999;45(10):1271–84.
44. Teicher MH, Samson JA, Polcari A, McGreenery CE. Sticks, stones, and hurtful words: relative effects of various forms of childhood maltreatment. Am J Psychiatry. 2006 Jun;163(6):993-1000.
45. Teicher MH, Andersen SL, Dumont NL, Ito Y, Glod CA, Vaituzis C, Giedd JN. Childhood neglect attentuates development of the corpus callosum. Soc Neurosci Abstr 2000;26:549.
46. Teicher MH, Ito Y, Glod CA, Andersen SL, Dumont N, Ackerman E. Preliminary evidence for abnormal cortical development in physically and sexually abused children using EEG coherence and MRI. Ann NY Acad Sci 1997;821:160–75.
47. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. Neurosci Biobehav Rev. 2003 Jan-Mar;27(1-2):33-44.
48. Welberg LA, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain. J Neuroendocrinol 2001;13(2): 113–28.
49. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology. 2008 Jul;33(6):693-710.
50. Carpenter LL, Tyrka AR, McDougle CJ, Malison RT, Owens MJ, Nemeroff CB, Price LH. Cerebrospinal fluid corticotropin-releasing factor and perceived early-life stress in depressed patients and healthy control subjects. Neuropsychopharmacology. 2004 Apr;29(4):777-84.
51. Heim C, Young LJ, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. Lower CSF oxytocin concentrations in women with a history of childhood abuse. Mol Psychiatry. 2009 Oct;14(10):954-8.
52. Andersen SL, Tomada A, Vincow ES, Valente E, Polcari A, Teicher MH. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. J Neuropsychiatry Clin Neurosci. 2008 Summer;20(3):292-301. doi: 10.1176/jnp.2008.20.3.292.
53. DE Bellis MD, Hooper SR, Spratt EG, Woolley DP. Neuropsychological findings in childhood neglect and their relationships to pediatric PTSD. J Int Neuropsychol Soc. 2009 Nov;15(6):868-78.
54. Kavanaugh BC, Dupont-Frechette JA, Jerskey BA, Holler KA. Neurocognitive deficits in children and adolescents following maltreatment: Neurodevelopmental consequences and neuropsychological implications of traumatic stress. Appl Neuropsychol Child. 2017 Jan-Mar;6(1):64-78.
55. van der Kolk BA. The neurobiology of childhood trauma and abuse. Child Adolesc Psychiatr Clin N Am. 2003 Apr;12(2):293-317, ix.
56. McCrory, E., De Brito, S. A., & Viding, E. (2011). The impact of childhood maltreatment: A review of neurobiological and genetic factors. Frontiers in Psychiatry, 2, Article 48.
57. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003 Jul 18;301(5631):386-9.
58. Kendler KS, Kuhn JW, Prescott CA. Childhood sexual abuse, stressful life events and risk for major depression in women. Psychol Med. 2004 Nov;34(8):1475-82.
59. Heim C, Bradley B, Mletzko TC, Deveau TC, Musselman DL, Nemeroff CB, Ressler KJ, Binder EB. Effect of Childhood Trauma on Adult Depression and Neuroendocrine Function: Sex-Specific Moderation by CRH Receptor 1 Gene. Front Behav Neurosci. 2009 Nov 6;3:41.
60. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, Tang Y, Gillespie CF, Heim CM, Nemeroff CB, Schwartz AC, Cubells JF, Ressler KJ. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA. 2008 Mar 19;299(11):1291-305.
61. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. Role of genotype in the cycle of violence in maltreated children. Science. 2002 Aug 2;297(5582):851-4.
62. McCrory E, De Brito SA, Viding E. Research review: the neurobiology and genetics of maltreatment and adversity. J Child Psychol Psychiatry. 2010 Oct;51(10):1079-95.
63. Kaufman J, Yang BZ, Douglas-Palumberi H, Grasso D, Lipschitz D, Houshyar S, Krystal JH, Gelernter J. Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. Biol Psychiatry. 2006 Apr 15;59(8):673-80.
64. Ressler KJ, Bradley B, Mercer KB, Deveau TC, Smith AK, Gillespie CF, Nemeroff CB, Cubells JF, Binder EB. Polymorphisms in CRHR1 and the serotonin transporter loci: gene x gene x environment interactions on depressive symptoms. Am J Med Genet B Neuropsychiatr Genet. 2010 Apr 5;153B(3):812-24.
65. Turecki G, Ota VK, Belangero SI, Jackowski A, Kaufman J. Early life adversity, genomic plasticity, and psychopathology. Lancet Psychiatry. 2014 Nov;1(6):461-6.
66. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci. 2009 Mar;12(3):342-8.
67. McGloin JM, Widom CS. Resilience among abused and neglected children grown up. Dev Psychopathol. 2001 Fall;13(4):1021-38.
68. Collishaw S, Pickles A, Messer J, Rutter M, Shearer C, Maughan B. Resilience to adult psychopathology following childhood maltreatment: evidence from a community sample. Child Abuse Negl. 2007 Mar;31(3):211-29.
69. Young, Jeffrey E; Klosko, Janet S; Weishaar, Marjorie E (2003). Schema therapy: a practitioner's guide. New York: Guilford Press.
70. Kessler, M. R. H., White, M. B., & Nelson, B. S. (2003). Group treatments for women sexually abused as children: A review of the literature and recommendations for future outcome research. Child Abuse & Neglect, 27(9), 1045–1061.
71. Stalker, C. A., & Fry, R. (1999). A comparison of short-term group and individual therapy for sexually abused women. The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie, 44(2), 168–174.
72. Briere, J. (2002). Treating adult survivors of severe childhood abuse and neglect: Further development of an integrative model. In J. E. B. Myers, L. Berliner, J. Briere, C. T. Hendrix, C. Jenny, & T. A. Reid (Eds.), The APSAC handbook on child maltreatment (p. 175–203). Sage Publications, Inc.
73. Paivio, S. C., & Nieuwenhuis, J. A. (2001). Efficacy of emotion focused therapy for adult survivors of child abuse: A preliminary study. Journal of Traumatic Stress, 14(1), 115–133.
74. Sandler IN, Ayers TS, Wolchik SA, Tein JY, Kwok OM, Haine RA, Twohey-Jacobs J, Suter J, Lin K, Padgett-Jones S, Weyer JL, Cole E, Kriege G, Griffin WA. The family bereavement program: efficacy evaluation of a theory-based prevention program for parentally bereaved children and adolescents. J Consult Clin Psychol. 2003 Jun;71(3):587-600.
75. Craighead, W. & Nemeroff C.B. (2005). The impact of early trauma on response to psychotherapy. Clinical Neuroscience Research. 4. 405-411.
76. Stevenson J. The treatment of the long-term sequelae of child abuse. J Child Psychol Psychiatry. 1999 Jan;40(1):89-111.
77. Nemeroff CB, Vale WW. The neurobiology of depression: inroads to treatment and new drug discovery. J Clin Psychiatry 2005; 66 (Suppl 7): 5–13.
78. Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, Mayberg H. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Arch Gen Psychiatry. 2004 Jan;61(1):34-41.
79. Heim C, Plotsky PM, Nemeroff CB. Importance of studying the contributions of early adverse experience to neurobiological findings in depression. Neuropsychopharmacology. 2004 Apr;29(4):641-8.
80. Keller MB, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342(20):1462-1470.
81. Nemeroff CB, Heim CM, Thase ME, Klein DN, Rush AJ, Schatzberg AF, Ninan PT, McCullough JP Jr, Weiss PM, Dunner DL, Rothbaum BO, Kornstein S, Keitner G, Keller MB. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. Proc Natl Acad Sci U S A. 2003 Nov 25;100(24):14293-6. doi: 10.1073/pnas.2336126100. Epub 2003 Nov 13. Erratum in: Proc Natl Acad Sci U S A. 2005 Nov 8;102(45):16530.
82. Pirkola S, Isometsä E, Aro H, Kestilä L, Hämäläinen J, Veijola J, Kiviruusu O, Lönnqvist J. Childhood adversities as risk factors for adult mental disorders: results from the Health 2000 study. Soc Psychiatry Psychiatr Epidemiol. 2005 Oct;40(10):769-77.
83. Agorastos A, Pervanidou P, Chrousos GP, Baker DG. Developmental Trajectories of Early Life Stress and Trauma: A Narrative Review on Neurobiological Aspects Beyond Stress System Dysregulation. Front Psychiatry. 2019 Mar 11;10:118.
84. Rutter M, Maughan B. Psychosocial adversities in childhood and adult psychopathology. J Pers Disord. 1997 Spring;11(1):4-18.

85. Putnam KT, Harris WW, Putnam FW. Synergistic childhood adversities and complex adult psychopathology. J Trauma Stress. 2013 Aug;26(4):435-42.
86. Richard P. Bentall, Charles Fernyhough. Social Predictors of Psychotic Experiences: Specificity and Psychological Mechanisms, Schizophrenia Bulletin, Volume 34, Issue 6, November 2008, Pages 1012–1020.